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High Incidence of Appropriate Implantable Cardioverter-Defibrillator Therapy in Patients With Syncope of Unknown Etiology and Inducible Ventricular Arrhythmias

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Objectives. **This study evaluates the hypothesis that in patients with syncope of unknown origin, inducible ventricular arrhythmias are specific arrhythmias and therefore should be appropriately treated.**

Background. **Although syncope is a common clinical entity, the evaluation and treatment of patients with syncope without a clear etiology are not well defined. Many patients with syncope of undetermined origin undergo invasive electrophysiologic evaluation. Abnormalities of the sinus node, prolongation of conduction times or inducible arrhythmias found at these evaluations are usually assumed to be the cause of syncope and are therefore treated. However, whether tachyarrhythmias are truly the cause of syncope, and whether treatment of these tachyarrhythmias can prevent recurrent syncope and arrhythmic death, is unknown.**

Methods. **This study included 50 consecutive patients with syncope of undetermined origin, ventricular tachyarrhythmias at electrophysiologic evaluation and treatment with an implantable cardioverter-defibrillator.**

Results. **Ventricular stimulation led to sustained monomorphic ventricular tachycardia in 36 patients, nonsustained ventricular tachycardia in 5 and ventricular fibrillation in 9. Over a 23 ± 15-month (mean ± SD) follow-up period, 18 patients received appropriate implantable cardioverter-defibrillator shock. Actuarial probability of appropriate therapy was 22% at 1 year and 50% at 3 years. Recurrent syncope was seen in five patients, three of whom had appropriate defibrillator detections at the time of syncope. Four patients died (sudden death in one, congestive heart failure in two).**

Conclusions. **In patients with syncope of undetermined origin and inducible ventricular tachyarrhythmias, appropriate implantable cardioverter-defibrillator therapy is common at follow-up. Sudden cardiac death is uncommon. This low incidence of sudden cardiac death and high incidence of appropriate defibrillator therapy support the current practice of using implantable cardioverter-defibrillators in patients with syncope of unknown origin and inducible ventricular arrhythmias.**

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Syncope is a common clinical complaint, representing up to 3% of emergency room visits and up to 6% of hospital admissions (1–3). In up to 50% of patients, no diagnosis can be made (2,4,5). Because of the frequent difficulty in determining the etiology of syncope and the potentially serious nature of arrhythmias, electrophysiologic testing was introduced as part of the evaluation in selected patients with syncope of unknown origin. Electrophysiological test results were found (6) to be abnormal in 20% to 75% of patients with syncope of unknown origin. The highest yield was found in patients with structural heart disease or electrocardiographic (ECG) abnormalities (6). Ventricular arrhythmias account for up to 50% of the electrophysiologic abnormalities identified in patients with syncope of unknown origin (7–21). Before the widespread use of implantable cardioverter-defibrillators, patients with syncope and inducible ventricular tachyarrhythmias were primarily treated pharmacologically (6). More recently, inducible ventricular tachyarrhythmias refractory to pharmacologic therapy in patients with syncope have become an accepted indication for implantation of a cardioverter-defibrillator (22). However, there are limited data demonstrating that patients with syncope and inducible ventricular tachyarrhythmias have an increased risk of spontaneous ventricular tachyarrhythmias. The natural history (and therefore specificity of inducible arrhythmias) of untreated patients with syncope and inducible ventricular arrhythmias is unknown. Although studies in untreated patients cannot be performed, implantable cardioverter-defibrillators provide the opportunity to examine the incidence of ventricular arrhythmias in the absence of antiarrhythmic agents. The present study focused on a group of patients with syncope, a nondiagnostic noninvasive workup, inducible ventricular arrhythmias and an implantable cardioverter-defibrillator. We hypothesized that these patients would have a high recurrence of ventricular arrhythmias. Therefore, we evaluated the outcome and specificity of induc-

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Abbreviations and Acronyms

AV = atrioventricular
ECG = electrocardiographic, electrocardiogram
NSVT = nonsustained ventricular tachycardia
NYHA = New York Heart Association
SMVT = sustained monomorphic ventricular tachycardia
VF = ventricular fibrillation
VT = ventricular tachycardia

ible ventricular arrhythmias in this patient group and assessed the appropriateness of implantable cardioverter-defibrillators therapy in these patients.

Methods

Study patients. The study included consecutive patients from January 1991 to December 1995 who presented with syncope or presyncope, had inducible ventricular arrhythmias at electrophysiologic evaluation and were treated with implantable cardioverter-defibrillators. Patients with sudden cardiac death or spontaneous sustained ventricular tachyarrhythmias were excluded. Patients received a complete noninvasive workup, including history and physical examination, routine blood tests, electrocardiography, echocardiography and 24 h of ambulatory ECG monitoring. Abnormalities found on noninvasive testing that could explain the patient's syncope or ventricular tachycardia (VT) >30 beats on prolonged ECG monitoring excluded the patient from the study.

Electrophysiologic evaluation. The initial drug-free electrophysiologic study was performed in the fasting, nonsedated state. All drugs with antiarrhythmic activity had been discontinued for at least 5 drug half-lives. Sinus node evaluation consisted of the measurement of sinus node recovery time at three cycle lengths (600, 500 and 400 ms) and measurement of sinoatrial conduction time. Premature atrial stimulation was performed to define the presence of dual-atrioventricular (AV) node physiology and to assess for atrial arrhythmias. Programmed ventricular stimulation included single and double ventricular extrastimuli during sinus rhythm and three basic drive cycle lengths, followed by triple extrastimuli during sinus rhythm and one drive cycle length (23). Our protocol for patients with syncope of unknown origin included programmed extrastimuli at the right ventricular apex and did not include testing during isoproterenol infusion. *Sustained monomorphic VT* (SMVT) was defined as VT >30 s or requiring termination because of hemodynamic compromise. *Nonsustained VT* (NSVT) was defined as VT lasting ≥10 beats. *Ventricular fibrillation* (VF) was defined as an arrhythmia of ventricular origin with a cycle length <220 ms requiring cardioversion.

Treatment. Patients with inducible ventricular arrhythmias underwent electrophysiologic-guided serial antiarrhythmic drugs trials performed in an attempt to identify an efficacious drug. Those patients with an efficacious drug found and who were discharged with this drug therapy without an implantable cardioverter-defibrillator were excluded from the study. By definition, all patients included in our study had treatment with an implantable cardioverter-defibrillator. Pharmacologic therapy in our study group was reserved for those patients with frequent NSVT, frequent implantable cardioverter-defibrillator shocks or atrial arrhythmias.

Clinical follow-up. After hospital discharge, the patients were followed up at regular intervals by their referring cardiologist and at our arrhythmia center every 3 months. Any symptoms of syncope, arrhythmia recurrence or implantable cardioverter-defibrillator discharge were noted and evaluated. Evaluation in those patients with implantable cardioverter-defibrillators with stored electrograms and RR intervals consisted of full interrogation and recovery of the episode.

Statistical analysis. All continuous variables are reported as mean value ± SD. Log rank survival tests were used to determined statistically significant ($p < 0.05$) differences of categoric variables. Continuous variables were analyzed using Cox proportional hazards models. Cox proportional hazards models were used to estimate relative risks. Thirty-one clinical variables were analyzed to assess predictors of recurrent arrhythmias, recurrent syncope and total mortality. These variables included age and type and presence of structural heart disease, New York Heart Association (NYHA) heart failure class, severity of coronary artery disease, ejection fraction, type of induced arrhythmia and discharge with a beta-adrenergic blocking or antiarrhythmic agent. All variables were initially analyzed separately; multivariate analysis was then performed for the variables that achieved statistical significance. Kaplan-Meier curves were constructed for syncope, appropriate implantable cardioverter-defibrillator therapy and survival.

Results

Patients. During the study duration, a total of 283 patients underwent electrophysiologic testing for syncope or presyncope of unknown origin. Of these patients, 66% had structural heart disease. At electrophysiologic testing, 82 patients had an inducible ventricular arrhythmia. A total of 50 of these patients received an implantable cardioverter-defibrillator and thus met our entry criteria. Of the remaining 32 patients, 15 were given antiarrhythmic agents (amiodarone in 4, other antiarrhythmic agents in 11); 6 patients underwent ablative procedures (surgical resections in 4, radiofrequency ablation in 2); VT was noninducible after coronary artery bypass graft surgery in 2 patients; 2 patients underwent orthotopic heart transplantation; and 7 patients (all with VF during triple extrastimuli with tight coupling intervals) were not treated. Of the 50 patients with an implantable cardioverter-defibrillator, 42 presented with syncope, and the remaining 8 with presyncope (40 men, 10 women; mean age 59 ± 14 years, range 28 to 80). Structural heart disease was present in 46 patients, with coronary artery disease in 33 and idiopathic dilated cardiomyopathy in 7. In addition, three patients had hypertrophic cardiomyopathy, two

Table 1. Electrophysiologic Study Results

No. of Extrastimuli	Induced Arrhythmia (no. of pts)		
	SMVT	NSVT	VF
1	1		
2	23	4	6
3	12	1	3

NSVT = nonsustained ventricular tachycardia; pts = patients; SMVT = sustained monomorphic ventricular tachycardia; VF = ventricular fibrillation.

had arrhythmogenic right ventricular dysplasia, one had congenital heart disease, and one had a benign cardiac tumor.

Noninvasive evaluation. All patients had a baseline ECG and admission blood work and underwent prolonged ECG monitoring. Baseline ECG abnormalities were common and included 9 patients with first-degree AV block and 13 with bundle branch blocks. Prolonged ECG monitoring demonstrated NSVT in 26 patients (mean 8 ± 6 beats, range 2 to 25). Signal-averaged ECG abnormalities were present in 17 of 27 patients who underwent this test. Mean left ventricular ejection fraction was 36 ± 14% (range 10% to 49%). No patient had significant aortic stenosis.

Electrophysiologic evaluation. At electrophysiologic testing, three patients had prolongation of sinus node function recovery (≥1.4 s). The mean HV interval was 58 ± 17 ms; the HV interval was prolonged (≥90 ms) in four patients. Ventricular stimulation resulted in SMVT in 36 patients, reproducible symptomatic NSVT in 5 and VF in 9 (Table 1). Mean cycle length of the induced monomorphic VT was 240 ± 42 ms. Only 1 patient had an induced arrhythmia (SMVT) with one extrastimulus, whereas 33 had their arrhythmia (SMVT in 23, NSVT in 4, VF in 6) induced with double extrastimuli and 16 with triple extrastimuli (SMVT in 12, NSVT in 1, VF in 3). Serial antiarrhythmic drug testing (mean 1.6 ± 0.7 drugs) was performed in 48 patients.

Treatment. All patients underwent cardioverter-defibrillator implantation. Event recording capability was present in 33 of these implantable cardioverter-defibrillators. Patients with non-event recording implantable cardioverter-defibrillators were treated earlier in the series. Concomitant coronary artery bypass graft surgery was performed in nine patients. Antiarrhythmic agents were used at the time of discharge in 18 patients. The indication for antiarrhythmic therapy was atrial fibrillation in 4 patients and frequent NSVT in the remaining 14.

Follow-up. All patients were followed up by their referring physician and at our arrhythmia center. During a mean follow-up period of 23 ± 15 months (range 1 to 56), 18 patients had 36 appropriate implantable cardioverter-defibrillator discharges defined as syncope or presyncope preceding defibrillator shock or ventricular tachyarrhythmia documented by event recorders (Fig. 1). Of the 33 patients with event recorder implantable-cardioverter defibrillators, 9 had appropriate implantable cardioverter-defibrillator discharges. The event recorders showed VT in seven patients with a mean cycle length of 282 ± 39 ms (range 240 to 360) and VF in two. Of the 17 patients without event recorder implantable cardioverter-defibrillators, a total of 9 had implantable cardioverter-defibrillator discharges preceded by syncope or presyncope. There was no statistical difference between arrhythmia recurrence in patients with and without event recorders. Actuarial analysis showed that the risk of appropriate implantable cardioverter-defibrillator discharges was 22% at 1 year, 32% at 2 years, 50% at 3 years and 85% at 4 years (Fig. 1).

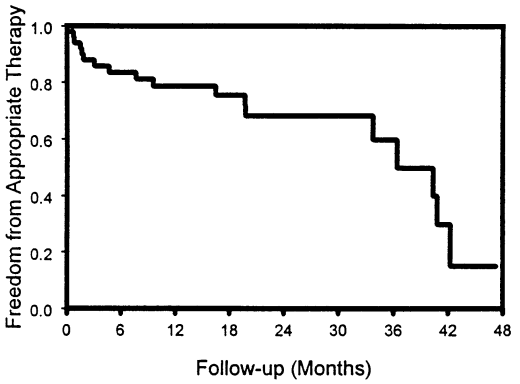

Figure 1. Kaplan-Meier life-table curve demonstrating high frequency of appropriate implantable cardioverter-defibrillator therapy in patients with syncope of unknown origin, inducible ventricular arrhythmias and treatment with implantable cardioverter-defibrillators. Appropriate therapy is defined as therapy preceded by syncope or presyncope (in patients with nonevent recording implantable cardioverter-defibrillators) or RR intervals and electrograms consistant with VT or VF.

Recurrent syncope was seen in five patients. Three of the five patients had implantable cardioverter-defibrillator discharges or detections of ventricular arrhythmias during their syncopal event. Two others had no detection of tachyarrhythmias by their implantable cardioverter-defibrillators. One of these patients was thought to have had a seizure, whereas the other patient's syncopal event was undiagnosed.

Four patients died (congestive heart failure in two at 2 and 17 months; sepsis at 25 months in 1; sudden death at 26 months in 1). The sudden death occurred in a patient with severe coronary artery disease who was found dead at home. His implantable cardioverter-defibrillator was not interrogated after his death.

Statistical analysis. Of the 31 variables evaluated (see Methods), the only statistically significant predictor of appropriate implantable cardioverter-defibrillator discharge was a shorter cycle length of induced arrhythmia (233 vs. 252 ms) during electrophysiologic testing ($p = 0.03$) (Table 2). Trends toward significance were seen in patients with inducibility at an earlier stage of ventricular stimulation ($p = 0.06$), Q waves on the admission ECG ($p = 0.07$) and discharge without antiarrhythmic therapy ($p = 0.09$). Those patients discharged with antiarrhythmic agents had a 1- and 2-year therapy incidence of 10% and 18% versus 28% and 44% in those discharged without antiarrhythmic agents. Presentation with syncope or presyncope, etiology of heart disease, duration of spontaneous NSVT, left ventricular ejection fraction and type of induced

Table 2. Predictors of Appropriate Implantable Cardioverter-Defibrillator Therapy

Variable	p Value	RR
Shorter cycle length of induced arrhythmia	0.03	1.17/10 ms*
Fewer extrastimuli to induce arrhythmia	0.07	0.36
Q waves on admission ECG	0.07	0.43
Discharge without AAD	0.09	0.39
SAECG abnormalities	0.11	4.6
Left ventricular ejection fraction	0.60	0.99
Etiology of heart disease	0.77	0.99
Type of arrhythmia induced		
NSVT	0.93	1.0
SMVT		1.48
VF		1.50
Event recording ICD or not	0.94	0.99

*Relative risk (RR) of 1.17 for each 10-ms change in cycle length. AAD = antiarrhythmic drug; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; SAECG = signal-averaged ECG.

arrhythmia were not significant predictors of appropriate implantable cardioverter-defibrillator therapy. Of the 36 patients with SMVT at baseline electrophysiologic testing, 14 had appropriate therapy. One of five patients with NSVT at electrophysiologic testing and three of nine patients with VF had an appropriate shock (Table 3).

With only one sudden death, no predictors of this event can be identified. Similarly, with the low event rates of recurrent syncope and all-cause mortality, predictors of these events are less reliable. Significant predictors of syncope recurrence were seen in patients with chronic AF ($p = 0.03$), lower left ventricular ejection fraction ($p = 0.03$) and concomitant coronary artery bypass graft surgery ($p = 0.04$). Significant predictors of all-cause mortality were previous coronary artery bypass graft surgery ($p = 0.01$), a higher NYHA congestive heart failure ($p = 0.01$) and Canadian Cardiovascular Society anginal class ($p = 0.01$) and chronic AF ($p = 0.04$) (Table 4). Trends for increased mortality were seen with Q waves on the ECG ($p = 0.08$) and discharge with a beta-blocker ($p = 0.09$).

Discussion

There have been only limited previous reports of long-term follow-up of patients with syncope of unknown origin, inducible ventricular tachyarrhythmias at electrophysiologic testing and treatment with implantable cardioverter-defibrillators. This population offers a unique opportunity to evaluate the clinical strategy of electrophysiologic testing in patients with unexplained syncope and the efficacy of implantable cardioverter-defibrillator therapy in patients with inducible ventricular arrhythmias. Most of the previously published series of electrophysiologic testing in syncope of unknown origin have had a limited number of patients with inducible ventricular arrhythmias. Follow-up in the group of patients with ventricular arrhythmias is often not separated from the patients that are found to have bradyarrhythmias or supraventricular arrhythmias. In fact, the present study is (to our knowledge) the largest series of patients with syncope, inducible ventricular tachyarrhythmias at electrophysiologic testing and treatment of any type.

Table 3. Patients with Appropriate Therapy According to Initial Electrophysiologic Study Results

No. of Extrastimuli	Induced Arrhythmia (no. of pts)		
	SMVT	NSVT	VF
1	1/1		
2	9/23	1/4	3/6
3	4/12	0/1	0/3

Abbreviations as in Table 1.

Table 4. Predictors of All-Cause Mortality

Variable	p Value
Higher NYHA congestive heart failure class	0.01
Higher CCS anginal class	0.01
Previous CABG	0.01
Presenting arrhythmia of atrial fibrillation	0.04
Q waves on admission ECG	0.07
Discharge on beta-blockers	0.08

CABG = coronary artery bypass graft surgery; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; NYHA = New York Heart Association.

Previous studies: electrophysiologic protocols and incidence of ventricular arrhythmias. Studies of electrophysiologic testing in patients with syncope of unknown origin show up to a 53% incidence of ventricular tachyarrhythmias (6). Marked variability of inducibility is seen and is most likely attributable to patient selection and ventricular stimulation protocol. Series of syncope of unknown origin with a higher degree of structural heart disease generally have higher inducibility rates (7,9,10,17). Within each series, patients with structural heart disease have a higher incidence of inducibility (6). The ventricular stimulation protocol is of prime importance for the sensitivity and specificity of induced arrhythmias. In patients with previously documented SMVT, sensitivities of 60% to 80% are seen with single and double extrastimuli (24–26) and 80% to 95% with the addition of a third extrastimulus (10,25,27). The true specificity of ventricular stimulation is more difficult to ascertain, but it is generally thought that the induction of SMVT is relatively specific (24,26,28). With more aggressive protocols, VF and polymorphic VT become more common and are thought to be nonspecific, induced arrhythmias (10,25). The induction of VF is generally accepted as an appropriate end point only in those patients with a high suspicion of clinical VF (29–31).

Previously published series of syncope of unknown origin have used ventricular stimulation protocols of double (7,9,11,13,19,20,32,33) and triple extrastimuli (8,10,12,14–17,21). In series using double extrastimuli, ventricular arrhythmias were seen in 7% to 36% of patients (mean 19%). In series using triple extrastimuli, ventricular arrhythmias were seen in 9% to 53% of patients (mean 33%). Many series included VF as a positive result of electrophysiologic testing, and these

patients were treated in the same manner as those with SMVT or NSVT.

Our protocol for electrophysiologic testing in patients with syncope of undetermined origin includes triple extrastimuli in sinus rhythm and at one basic cycle length drive train (23). This protocol is similar to the protocol that many laboratories presently use (17,21). In our study, patients with inducible arrhythmias with fewer extrastimuli exhibited a trend for increased appropriate implantable cardioverter-defibrillator discharge (Table 2).

Previous studies: follow-up of patients with inducible arrhythmias. Previous follow-up data for the patients with syncope, a nondiagnostic, noninvasive workup and inducible ventricular arrhythmias at electrophysiologic testing are limited. The largest series of these patients to date was reported by Click et al. (15) in 1987. In that group of 112 patients presenting with syncope and bundle branch block, 46 had inducible ventricular arrhythmias with triple extrastimuli during ventricular pacing (SMVT in 25, NSVT in 19, VF in 2). All patients in the inducible ventricular tachyarrhythmia cohort were treated with antiarrhythmic agents or ablative operation. With a mean 30-month follow-up period, sudden cardiac deaths in the inducible ventricular arrhythmia group occurred frequently (11 patients). Seventeen additional patients had recurrent syncope, and four had recurrent SMVT. Bass et al. (16), in 1987, also reported high sudden cardiac death rates (14 of 35) in patients with ventricular arrhythmias found at electrophysiologic testing performed for syncope of undetermined origin. In that study, no difference in outcome was seen on the basis of rhythm (SMVT, NSVT or VF) induced at electrophysiologic testing. In contrast to the previous studies, Olshansky et al. (13) found a lower incidence of sudden death (3 of 28) in syncopal patients with inducible ventricular arrhythmias. Other smaller studies (8–10,17,20,33) have demonstrated a variable percent of sudden cardiac death (0% to 17%) during follow-up in the cohort with syncope of undetermined origin found to have ventricular tachyarrhythmias at electrophysiologic testing. Only two small series (18,21) have reported treatment with an implantable cardioverter-defibrillator. In these two series, a total of 7 of 11 patients treated with implantable cardioverter-defibrillators had appropriate therapy.

In our patients with syncope and inducible ventricular arrhythmias, we found a 50% incidence of appropriate implantable cardioverter-defibrillator shocks at 3 years of follow-up, which suggests a high incidence of ventricular arrhythmia recurrence. This finding is similar to the ventricular arrhythmia recurrence rate found in patients who received an implantable cardioverter-defibrillator after presenting with cardiac arrest or SMVT (34–36). In our series, the incidence of sudden cardiac death was low (2%), which is similar to or lower than that in patients who present with cardiac arrest or SMVT (34–36). However, in the previously described large series of patients with syncope and inducible arrhythmias, the incidence of sudden cardiac death ranged from 11% to 40% (13,15,16). The low sudden cardiac death rate in our patient cohort and the high incidence of appropriate implantable cardioverter-defibrillator therapy suggest that the implantable cardioverter-defibrillator may be effective in saving lives in patients with syncope and inducible ventricular arrhythmias. Whether implantable cardioverter-defibrillator therapy truly reduces overall mortality in this group of patients can only be answered with a prospective, randomized trial. However, only the Canadian Implantable Defibrillator Study (CIDS) (37) includes patients with syncope of unknown origin and inducible ventricular arrhythmias. Neither the Antiarrhythmics Versus Implantable Defibrillators (AVID) (38) nor the Cardiac Arrest Study Hamburg (CASH) (39) includes patients with syncope of unknown origin and inducible ventricular arrhythmias. Therefore, prospective, randomized data for this group of patients will be limited.

Patients with induced VF. The treatment of patients with inducible VF and syncope of unknown origin is controversial. During the time period of our study, 16 patients with syncope of unknown origin had inducible VF at electrophysiologic testing, 9 of whom had implantation of a cardioverter-defibrillator. Of these nine patients, seven had runs of NSVT or nonsustained VF preceding their sustained VF. Three of the patients with inducible VF had appropriate implantable cardioverter-defibrillator discharges. The seven patients with inducible VF who did not receive an implantable cardioverter-defibrillator had VF induced with tight coupling intervals with three extrastimuli, and only one had reproducible NSVT or VF. Our finding that VF induced with double extrastimuli may be associated with arrhythmia recurrence is consistent with other series of syncope of unknown origin demonstrating a high rate of recurrent syncope and sudden death in patients with inducible VF (16,21). It is possible that inducible VF in the patient population presenting with syncope is not as nonspecific as has been previously suggested.

Limitations of the study. Limitations to our study include the retrospective analysis of patient outcomes. Inclusion of patients without event recording implantable cardioverter-defibrillators (n = 17) and therefore reliance on symptoms before implantable cardioverter-defibrillator shock to classify discharge as appropriate are additional limitations. Finally, the use of antiarrhythmic agents in 36% of our patients could affect implantable cardioverter-defibrillator discharge incidence.

Conclusions. Patients with unexplained syncope and inducible ventricular arrhythmias at electrophysiologic testing have a high incidence of appropriate implantable cardioverter-defibrillator therapy during follow-up. The high level of appropriate therapy argues for the specificity of electrophysiologic testing in this patient subgroup; however, the sensitivity of electrophysiologic testing cannot be determined from the present study. Sudden cardiac death rates were low in this cohort treated with implantable cardioverter-defibrillators. This low sudden cardiac death rate and high appropriate implantable cardioverter-defibrillator discharge rate support the current clinical practice of implanting cardioverter-defibrillators in patients with syncope of unknown origin and inducible ventricular arrhythmias.

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